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Severe preeclampsia goes along with a cytokine network disturbance towards a systemic inflammatory state

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ABSTRACT

Although preeclampsia causes high maternal/fetal morbidity and mortality, the etiology of this multi-system disorder still remains to be elucidated. Herein, we have characterized the cytokine plasma levels in severe preeclamptic women compared to normotensive pregnant and non-pregnant women, aiming to better understand the immunological network and its clinical significance for the pathogenesis and severity of preeclampsia. A total of 219 women were selected. The study population was composed of three groups referred as severe preeclamptic, normotensive pregnant and non-pregnant women. Cytokine plasma levels were determined using commercially available kits, Cytometric Beads Array – CBA to quantify TNF-α, IFN-γ, IL-4, IL-5, IL-10, IL-1β, IL-6, IL-8 and IL-12. Our findings demonstrated that severe preeclamptic state is associated with high levels of pro-inflammatory cytokines IL-8, IL-6, and IFN-γ ($P < 0.05$ for all) whereas normotensive pregnancy evolves high levels of regulatory cytokine IL-10 ($P < 0.05$). Moreover, an outstanding pro-inflammatory "cytokine signature" could be observed in severe preeclamptic women display, while an overall regulatory state is the hallmark for normotensive pregnancy. In summary, our data showed that elevated levels of pro-inflammatory cytokines in the maternal circulation with a deviation in the "IL-8 × IL-6" axis towards IFN-γ might drive the cytokine network in preeclamptic women towards an excessive systemic inflammatory state.

1. Introduction

Preeclampsia (PE) is a multifactorial disease characterized by systolic blood pressure ⩾140 mmHg or diastolic ⩾90 mmHg at bed rest on at least two occasions 6 h apart, and proteinuria ⩾0.3 g/24 h, measured after the 20th week of pregnancy [1]. Clinically, it is important to diagnose the severe form of PE when hypertension and proteinuria are even higher. This form can progress to eclampsia (characterized by seizures as a sign of affection of the cerebral vessels), HELLP syndrome (hemolysis, elevated liver enzyme, low platelets) or disseminated intravascular coagulation [2].

Although PE causes high maternal/fetal morbidity and mortality, the etiology of this multi-system disorder still remains to be elucidated.

It is well established that the physiological balance between pro-inflammatory/regulatory responses presents important changes in healthy pregnancy, with a shift toward a regulatory state [3]. In PE it has been proposed that this alteration does not occur, or it is reverted in very early stages of the disease, and in consequence, it leads to a pro-inflammatory state. Previous studies showed increased levels of IFN-γ and decreased levels of IL-4 [4–7]. On the other hand, regarding to TNF-α, IL-1β, IL-6, IL-8, and IL-10 conflicting results have been found [7–13].

In the present investigation, we have characterized the wide cytokine profile in severe preeclamptic women, compared to normotensive pregnant and non-pregnant women, aiming to better understand the immunological network and its clinical significance for the PE pathogenesis and severity.

2. Materials and methods

2.1. Study population

A total of 219 women were selected from Odete Valadares Maternity-Belo Horizonte/Brazil, Regional Public Hospital of Betim/Brazil and Healthy Center Guanabara, Betim/Brazil from 2009 to 2011. The study population was composed of three groups

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referred as severe preeclamptic, normotensive pregnant and non-pregnant women. The severe preeclamptic group comprises 69 women, age ranging from 14 to 44 years, with gestational age between 22 and 40 weeks. Severe PE was defined by systolic blood pressure $\geqslant$160 mmHg or diastolic blood pressure $\geqslant$110 mmHg, on more than two consecutive occasions within 4 h apart and proteinuria >2 g L^{-1} or at least 2+ protein by dipstick. The group of normotensive pregnant was composed by 69 women, age ranging from 14 to 42 years, with gestational age between 20 and 41 weeks with systolic/diastolic blood pressure below 120/80 mmHg and no history of hypertension or proteinuria. Non-pregnant women, with age ranging from 14 to 44 years, had no clinical and laboratory alterations. No significant differences were observed for age and gestational age. As expected, significant differences were observed for body mass index (BMI), gestational weight gain (GWG) as well as systolic (SBP) and diastolic blood pressures (DBP). Table 1 summarizes the clinical characteristics of the study groups.

Exclusion criteria common for the three groups were chronic hypertension, haemostatic abnormalities, cancer, diabetes, cardiovascular, autoimmune, renal, and hepatic diseases, anticoagulant or corticosteroids therapy.

The Ethics Committee at Federal University of Minas Gerais-Brazil approved this study and informed consent was obtained from all participants. The research protocol did not interfere with any medical recommendations or prescriptions.

2.2. Blood sampling

Five mL whole blood samples were drawn in EDTA-K_3 1.8 mg/mL (Vacuette®) and centrifuged at 2500*g* for 20 min at 4 °C to obtain the plasma samples. Aliquots were stored at −70 °C until use for flow cytometric cytokine measurements.

2.3. Cytometric beads array for cytokine measurements

Cytokine plasma levels were determined using commercially available kits, including Human Th1/Th2 Cytometric Beads Array – CBA (BD Biosciences Pharmingen, USA) to quantify TNF-α, IFN-γ, IL-4, IL-5 and IL-10 along with the Human Inflammation kit to quantify IL-1β, IL-6, IL-8 and IL-12. The CBA immunoassay was carried out according to the manufacturer instructions.

2.4. Analysis of "cytokine plasma levels" and "cytokine signatures"

The cytokine plasma levels were analyzed as the mean fluorescent intensity (MFI) provided by the CBA immunoassay. Additionally, the analysis referred as "cytokine signatures" were also performed as previously proposed by Luiza-Silva et al. [14]. Briefly, the global median value for each cytokine was used as the cut-off edge to tag each women as they display "Low levels" (▭ for all cytokines), "High levels of pro-inflammatory" (■ for IL-8, IL-6, IL-1β, TNF-α, IL-12, and IFN-γ) or "High levels of regulatory" (▭ for IL-4, IL-5, and IL-10) cytokines. The frequency (%) of women showing "High cytokine levels" was calculated and the "cytokine signature" assembled as the ascendant frequencies in order to identify changes in the overall cytokine patterns amongst the three studied groups.

2.5. Statistical analysis

Demographic and clinical characteristic were compared amongst subgroups by ANOVA followed by Tukey post-test. The cytokine plasma levels, expressed as medium fluorescence intensity (MFI), were compared amongst subgroups by Kruskal–Wallis followed by Dunn's post-test. All analysis were performed using the program GraphPad PRISM (version 5.0) and significant differences, in all cases, considered at $P < 0.05$.

Additional strategy of data analysis was used to compare the ascendant profile referred as "cytokine signatures". Relevant differences were considered when the frequency of patients with high cytokine levels was above the 50th percentile. Spearman's rank correlations (r_S) were computed to assess correlations between inflammatory cytokines IL-8, IL-6, IL-1β, TNF-α and IFN-γ in preeclamptic women, normotensive pregnant and non-pregnant women.

3. Results

3.1. Severe preeclamptic state is associated with high levels of pro-inflammatory cytokines IL-8, IL-6, and IFN-γ whereas normotensive pregnancy evolves with high levels of regulatory cytokine IL-10

The analysis of cytokine plasma levels for groups demonstrated that the levels of IL-8, IL-6 and IFN-γ were significantly higher in preeclamptic women as compared to non-pregnant women as well as to non-pregnant women (Fig. 1). Moreover, the levels of TNF-α were also significantly higher in preeclamptic women in comparison with non-pregnant women. On the other hand, normotensive pregnant showed significantly higher levels of IL-10 as compared to preeclamptic women and non-pregnant. No significant differences were observed for plasma levels of the other cytokines evaluated.

3.2. Severe preeclamptic women display an outstanding pro-inflammatory "cytokine signature" while an overall regulatory state is the hallmark of normotensive pregnancy

In order to assemble the cytokine signature of each study group, the global median plasma values for each cytokine was first calculated to establish the cut-off used to segregated women with "Low" or "High" cytokines levels, as illustrated in Fig. 2A (IL-8 = 2.75; IL-6 = 9.31; IL-1β = 4.39; TNF-α = 4.03; IL-12 = 7.77;

Table 1
Demographic and clinical characteristics of the three studied groups.

Parameters	Non-pregnant	Normotensive pregnant	Preeclamptic women	*P* value
Age (years)	25 (6.2)	24 (6.2)	26 (7.1)	0.281
GA (weeks)	–	33 (20–41)	33 (22–40)	0.799
BMI (kg/m^2)	21.80 (19.95–25.45)	23.30 (21.00–26.70)	23.94 (21.69–28.03)[a]	0.016*
GWG (kg)	–	10.0 (0.1–25.4)	12.7 (2,1–76.1)	0.033*
SBP (mmHg)	120 (80–130)	110 (90–130)	170 (130–220)[a,c]	<0.001*
DBP (mmHg)	80 (50–90)	70 (50–90)	110 (90–150)[a,c]	<0.001*

GA: gestational age; GWG: gestational weight gain; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index (–): does not apply.
Age is expressed as mean (SD) and data analysis performed by ANOVA followed by Tukey post-test.
GA, GWG, BMI, SBP and DBP are expressed as median (min–max) and data analysis performed by Kruskal–Wallis followed by Dunn's post-test.
* Statistic significances at $P < 0.05$ are highlighted by: [a] non-pregnant *vs* PE; [b] non-pregnant *vs* normotensive pregnant; [c] normotensive pregnant *vs* PE.

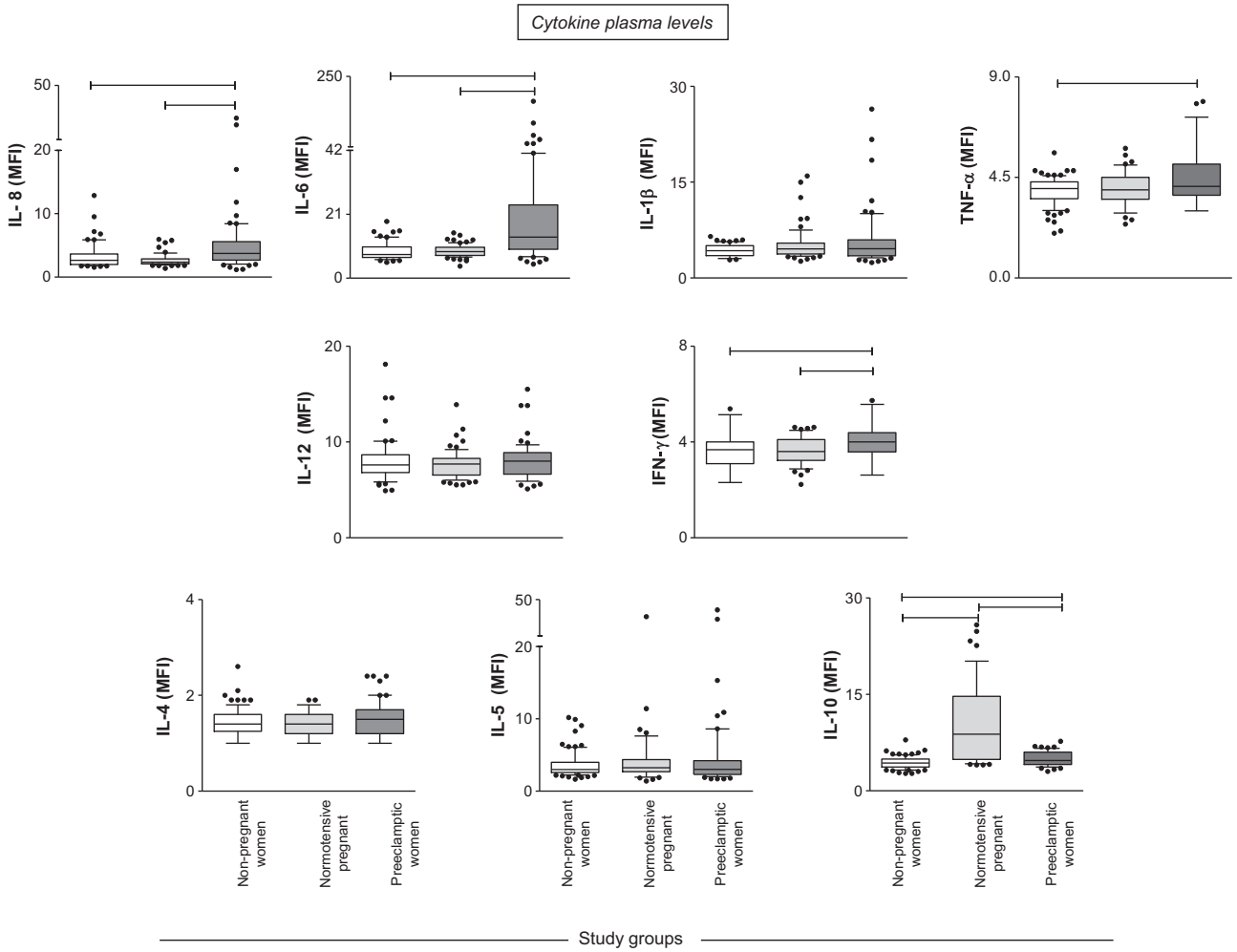

Fig. 1. Cytokine plasma levels in preeclamptic women (■) as compared to normotensive pregnant (▒) and non-pregnant women (□). Plasma levels of pro-inflammatory (IL-8, IL-6, IL-1β, TNF-α, IL-12, and IFN-γ) and regulatory (IL-4, IL-5, and IL-10) cytokines were determined by cytometric beads array. Results are expressed in mean fluorescence intensity (MFI) data are presented in a box plot format. The lines stretch from the 10th percentile to the upper 90th percentile, highlighting the outliers (●). The median is shown as a line across the box. Statistical analysis was performed by non-parametric Mann–Whitney test. Significant differences at $P < 0.05$ are highlighted by connecting lines.

IFN-γ = 3.79; IL-4 = 1.40; IL-5 = 3.13; IL-10 = 4.70, all expressed in MFI). Using these values, each woman received a tag for each cytokine. Following, diagrams were used to assemble the pro-inflammatory and regulatory profiles and to calculate the frequency (%) of women showing "High cytokine levels" as showed in the Fig. 2B. The frequency of women with high cytokine levels was further compiled to establish the cytokine ascendant profile, referred as "cytokine signatures" for each study group (Fig. 3A). Data analysis was carried out considering relevant only the cytokine frequencies above the 50th percentile. Using this criterion, the IL-4 was the only relevant element in the "cytokine signature" of the non-pregnant women. On the other hand, normotensive pregnant showed an outstanding frequency of regulatory cytokines IL-4, IL-5 and IL-10 along with borderline inflammatory IL-1β. Moreover, cytokine signatures of severe preeclamptic women showed a predominance of pro-inflammatory cytokines, including IL-8, IL-6, IL-1β, TNF-α, IL-12 and IFN-γ with IL-4 as the only one regulatory cytokine. The overlay of ascendant "cytokine signatures" from the three study groups was further used to illustrate these findings (Fig. 3B). Alternatively, the ascendant "cytokine signature" from the non-pregnant group was used as a reference curve for comparative analysis with the normotensive and severe PE groups (Fig. 4A). Considering relevant only the cytokine frequencies above the 50th percentile, data analysis demonstrated that the normotensive group displayed elevated percentage of women with high levels of IL-1β, IL-5 and IL-10 as compared to the non-pregnant group. On the other hand, severe preeclamptic group showed enhanced frequency of pro-inflammatory cytokines, including IL-8, IL-6, IL-1β, TNF-α, IL-12, and IFN-γ as compared to the non-pregnant women group (Fig. 4A).

Additionally, the severe preeclamptic group showed higher frequency of pro-inflammatory cytokines, including IL-8, IL-6, TNF-α, IL-12 and IFN-γ along with lower frequency of regulatory cytokines (IL-5 and IL-10) when the ascendant "cytokine signature" from the normotensive group was used as a reference curve for comparative analysis (Fig. 4B).

3.3. Deviation in the "IL-8 × IL-6" axis towards IFN-γ is the hallmark of the cytokine network correlation in preeclamptic women

The dynamic connections within the pro-inflammatory cytokine network were further evaluated using the correlation analysis as a tool to identify any shift in preeclamptic women aside from the normal pregnancy course (Fig. 5). Our data pointed out to a universal axis of positive correlation between IL-8 and IL-6 in all studied groups. In non-pregnant women this axis also included an effective correlation with TNF-α, whereas in normotensive pregnant this common axis shifted towards a connection with

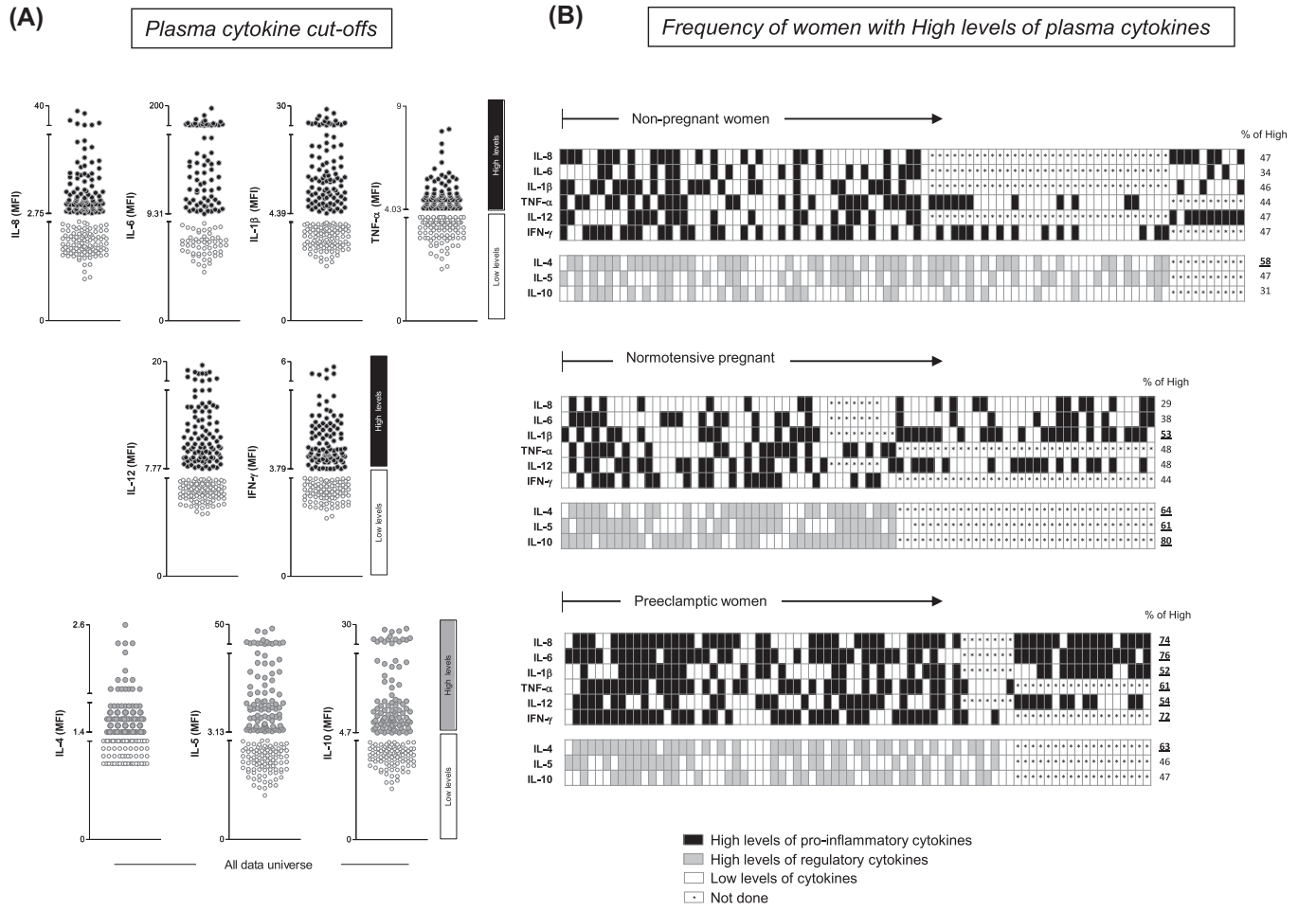

Fig. 2. Plasma cytokine cut-off and frequency of women with High levels of plasma cytokine amongst preeclamptic women, normotensive pregnant and non-pregnant women. (A) Scatter graphs employed to establish the concept of Low cytokine producers (○ < global median), High pro-inflammatory cytokine producers for IL-8, IL-6, IL-1β, TNF-α, IL-12, IFN-γ (● ⩾ global median) and High regulatory cytokine producers for IL-4, IL-5 and IL-10 (◍ ⩾ global median), all expressed in Mean fluorescence Intensity – MFI). Low (□ for all cytokines) and High (■ for pro-inflammatory and ▩ for regulatory) cytokine producers were tagged for further frequency analysis. (B) Multi-cytokine diagrams used to quantify the frequency of women with high levels of cytokines in all studied groups. Relevant frequencies, considered for values above the 50th percentile are highlighted in bold underline format.

IL-1β. Although the IL-1β connection is somehow preserved in preeclamptic women, a deviation forward IFN-γ appears as a satellite link reinforcing the pro-inflammatory cytokine network at this clinical condition.

4. Discussion

Our data demonstrated high levels of IL-8 in preeclamptic women comparing to normotensive pregnant. According, several studies showed higher IL-8 plasma levels in preeclamptic women [6,7,15]. Likewise, increased IL-8 production by maternal peripheral blood mononuclear cells (PBMCs) in PE has been demonstrated [16–19]. Production of IL-8 by neutrophils that infiltrate the vasculature in women with PE [20,21] would provide a chemotactic gradient to attract more neutrophils. These cells can adhere on the endothelium, infiltrate into the intimal space and release reactive oxygen species, myeloperoxidase, matrix metalloproteinase 8 and thromboxane, causing inflammation [22]. In this way, IL-8 seems to have a pivotal role in PE pathogenesis and severity.

Moreover, our data demonstrated high levels of IL-6 in preeclamptic women comparing to normotensive pregnant. Similarly, a recent metanalysis has highlighted the role of IL-6 in PE [13]. IL-6 is a multifunctional cytokine that regulates hematopoiesis, as well as the acute-phase reaction and modulates both pro- and anti-inflammatory events [23]. Chronic infusion of this cytokine to pregnant rats *in vivo* has caused hypertension and proteinuria, the two classical symptoms of PE [24,25]. Endothelium activation is associated with PE, which justifies, at least in part, the clinical signs of the disease [26]. As it is known that IL-6 interferes in endothelial cell function [27], a role of this cytokine in PE may be admitted. It has been shown that an increased level of circulating IL-6 levels occur in PE women regardless the gestational age (early or late) of PE onset [28]. These results suggested that an excessive maternal inflammatory response is associated with this disease.

TNF-α is a powerful pro-inflammatory cytokine and it is found in human placental and uterine cells, both early and late in gestation [29]. Several studies have reported elevated TNF-α maternal circulating levels in PE, suggesting that TNF-α could be involved in the pathogenesis of this disease [13,19,30–33]. However, likewise our data, other studies have not reported significant differences in TNF-α maternal levels compared to normotensive pregnant [16,17,34,35].

It is known that IL-6 can inhibit IL-1 and TNF-α [23,36], which could be one explanation for a lack of differences for the latter two cytokines between preeclamptic women and normotensive pregnant. Another justification may be due to the relatively short half-life of the cytokines, as well as possible transient and episodic release, which may result in considerable plasma levels variation not

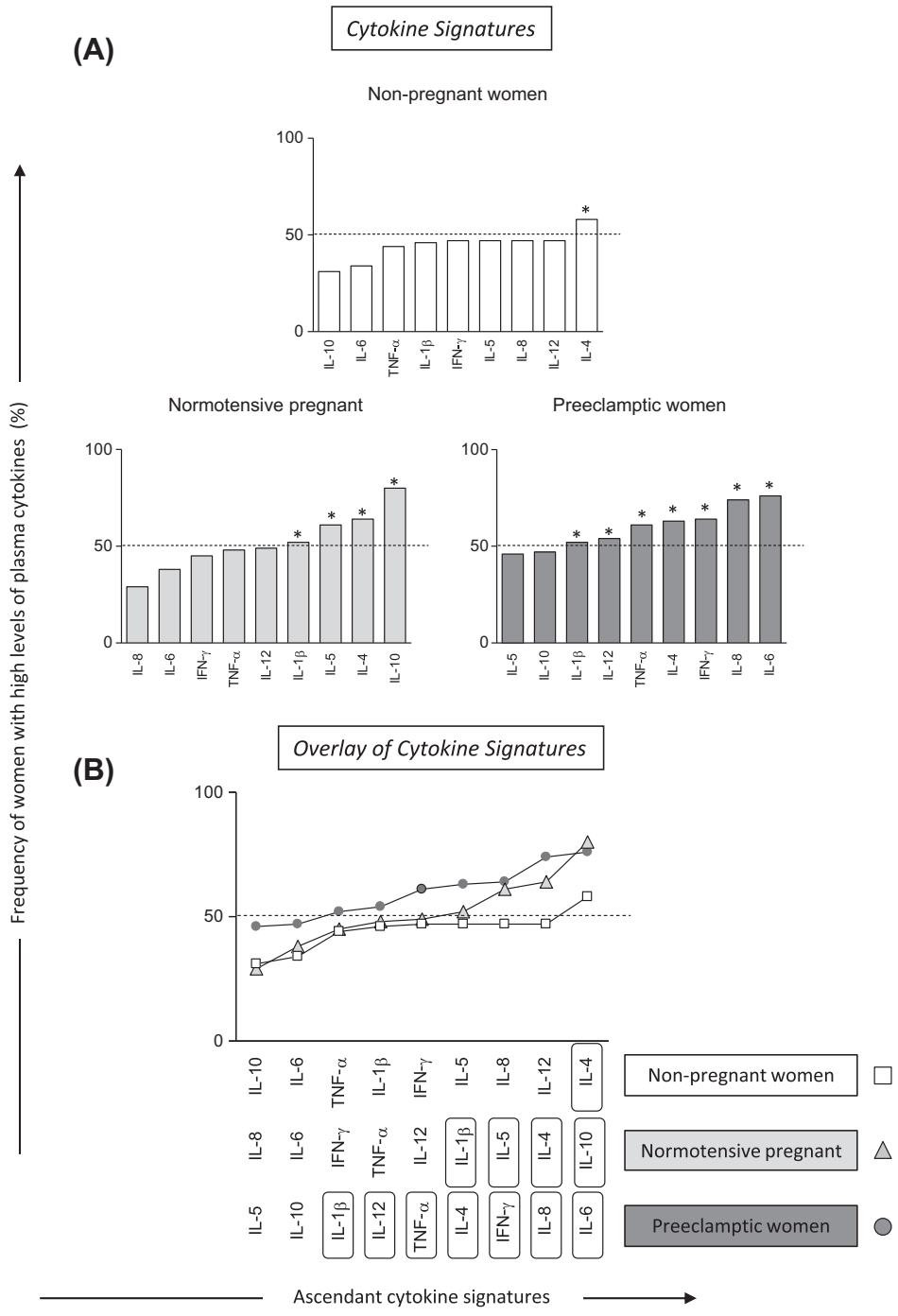

Fig. 3. "Cytokine signatures" preeclamptic women, normotensive pregnant and non-pregnant women. (A) The ascendant frequency of women with *High* levels of plasma cytokine was assembled and data expressed by bars graphs. Relevant frequencies, considered for values above the 50th percentile (cut-off dotted line) are highlighted by *. (B) The cytokine signatures were further overlaid for preeclamptic women (●), normotensive pregnant (△) and non-pregnant women (□) to identify relevant elements in the cytokine signature that emerge above the 50th percentile (cut-off dotted line). These elements are highlighted in the bottom "*X* axis" by rectangles.

shown in a single blood sample. Although IL-1 and TNF-α were not increased in preeclamptic women, it is known that the endothelium in some patients might be more sensitive to activation by cytokines, which could lead to injuries even when the cytokines levels are normal [17]. Little is known about the relationship between the cytokine profile and distinct clinical forms of PE (mild and severe), mainly due to insufficient studies on this matter. A recent report has demonstrated that there are no significant differences between the serum levels of TNF-α and IL-6 between mild and severe PE [37].

In agreement with our findings, several studies have been demonstrated high IFN-γ levels in preeclamptic women [5–7,38,39]. However, other studies have not found an increase in this cytokine levels in preeclamptic women compared to normotensive pregnant [4,17]. The role of IFN-γ during normal pregnancy is still controversial. For instance, primiparous IFN-γ knockout mice experience fetal loss [40], and this cytokine can trigger spiral artery modifications [41]. However, these results were not obtained in multiparous mice.

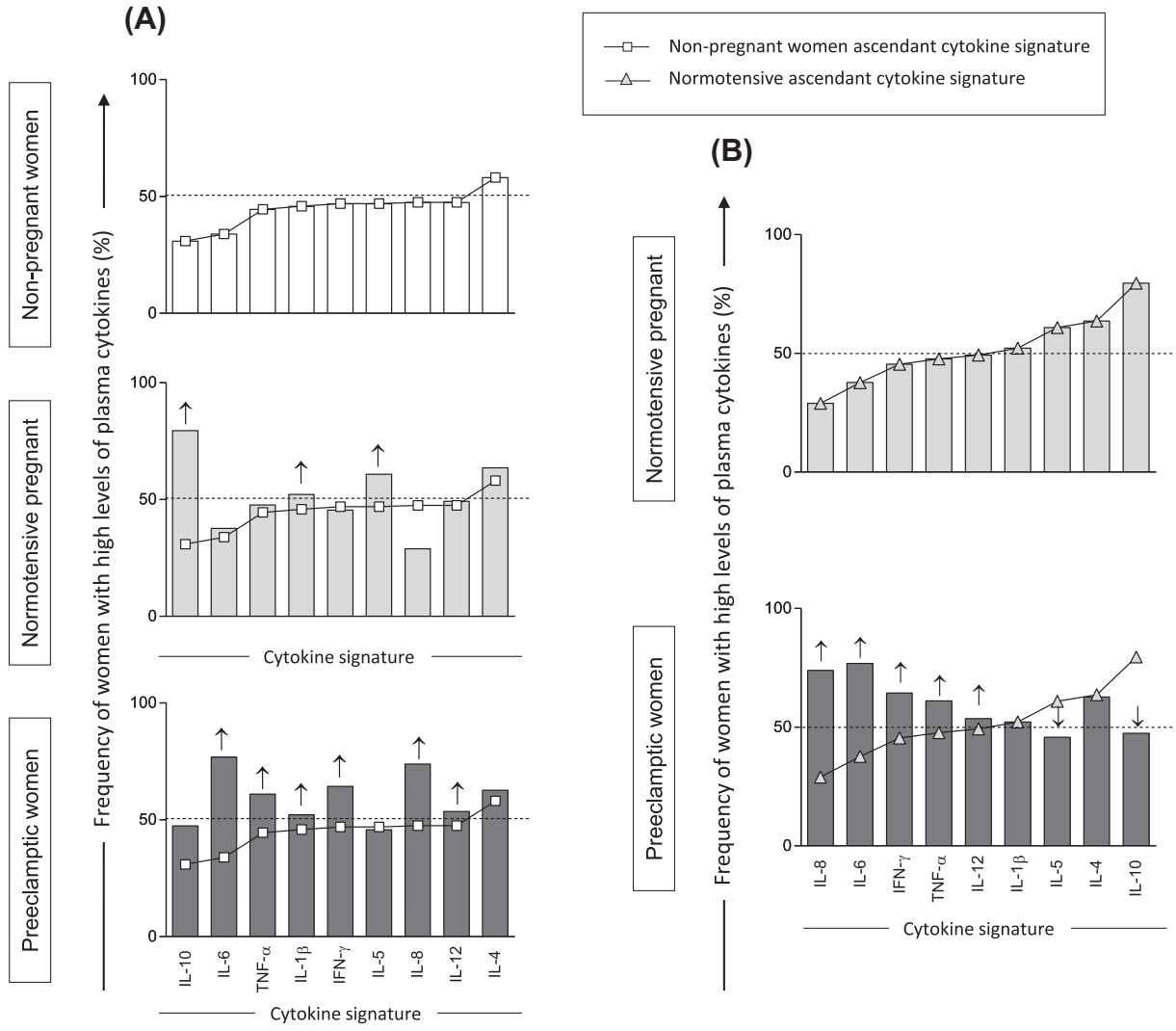

Fig. 4. Comparative analysis of the cytokine signatures of preeclamptic women as compared to normotensive pregnant (▒) and non-pregnant women. (A) The ascendant frequency of women with high cytokine plasma levels was assembled for the non-pregnant women as demonstrated by bars graphs (□) and by the ascendant cytokine curve for non-pregnant women (—□—). Comparative analysis with normotensive pregnant and preeclamptic women (■) was further performed taking the ascendant cytokine for non-pregnant women (—□—) as reference. (B) The ascendant frequency of women with high cytokine plasma levels was also assembled for the normotensive pregnant (—△—) and used for comparative analysis with the cytokine profile of preeclamptic women. Dotted lines indicate the 50th percentiles used as the cut-off to identify relevant elements, highlighted by ↑ and ↓ for increased or decreased frequencies, respectively.

Regarding IL-10, our results showed increased levels in normotensive pregnant compared to preeclamptic women and non-pregnant women (Fig. 1). Previous studies reported high levels of IL-10 in healthy pregnant [9,42–45], suggesting that successful pregnancy reflects a predominance of regulatory cytokine. Studies in mice revealed that IL-10 deficiency in early pregnancy affects trophoblast growth and differentiation, causing placental failure and abortion [46]. IL-10 also increases the resistance of trophoblasts to Fas-mediated apoptosis [47]. Inhibition of IL-10 by passive immunization (with monoclonal antibody to IL-10) during early gestation increases blood pressure in pregnant baboons [48]. Therefore, it has been suggested that decreased IL-10 production is associated with pregnancy disorders including PE [32,49,50].

Contrarily to our data other studies demonstrated an increase in IL-10 levels in preeclamptic women compared to normotensive pregnant [7,13,51,52]. The interpretation of IL-10 results should be cautiously done. As the half-life of this cytokine is very short, it is not consistently present in circulation. Therefore, a single blood sample may fail to detect a sporadic raise or decline in this cytokine level. Besides, other factors as the effect of gestational age at the time of sample collection, the influence of body mass index and the assay sensitivity may also explain the divergences in IL-10 levels among studies [53]. In conclusion, there is no consensus regarding IL-10 production in PE.

IL-1β, IL-12, IL-4, and IL-5 were successfully detected in our studied groups but no difference was found comparing preeclamptic women and normotensive pregnant. Although this might represent the real condition *in vivo*, such results must be carefully interpreted. A speculative explanation could be related to the paracrine action of T-cell cytokines, which are quickly bound to receptors on neighboring cells, not being available in circulation. As a result, these cytokines plasma levels in both groups may be similar, even though an increased production has occurred in PE [17].

The cytokine profile from the each group as a whole showed that normotensive pregnant presented an outstanding frequency of regulatory cytokines IL-4, IL-5 and IL-10, along with borderline inflammatory IL-1β, while for non-pregnant women only IL-4 was increased (Fig. 3). On the other hand, severe preeclamptic women showed a predominance of pro-inflammatory cytokines, including IL-8, IL-6, IL-1β, TNF-α, IL-12 and IFN-γ, while IL-4 was the only increased regulatory cytokine. These data suggest that severe PE is associated with an exacerbated inflammatory condition,

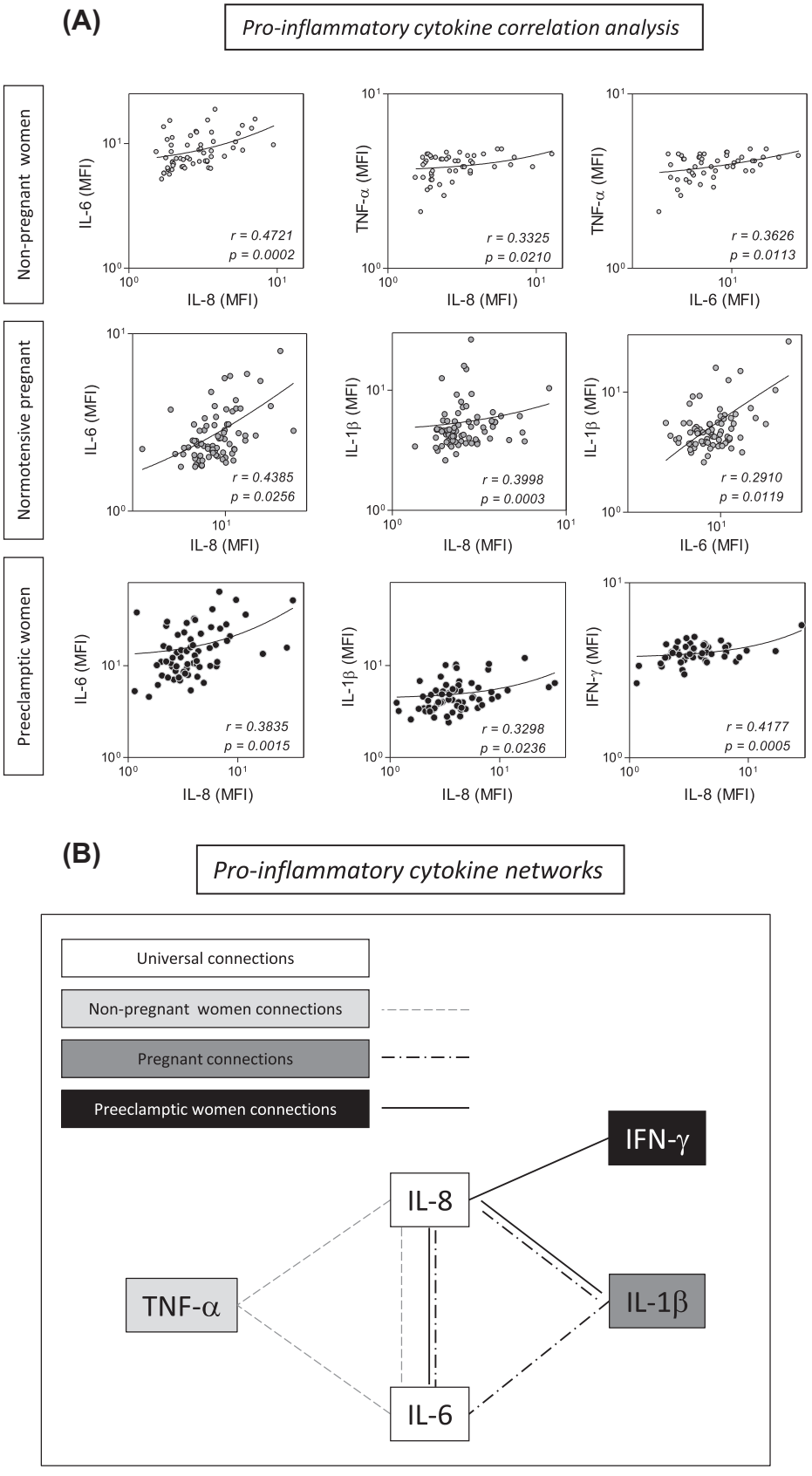

Fig. 5. Correlations analysis of pro-inflammatory cytokines in preeclamptic women as compared to normotensive pregnant and non-pregnant women. (A) Spearman correlation graphs illustrate the significant connections within the pro-inflammatory cytokine network. (B) The grayscale diagram point out the universal connections between IL-8 and IL-6 in all studied groups (▭). An effective association with TNF-α is observed in non-pregnant women (▭), whereas a shift towards IL-1β is observed during pregnancy (▭) as observed in normotensive pregnant and preeclamptic women. Deviation towards a satellite connection with IFN-γ (▭) is the hallmark of preeclamptic women. The cytokine network links are represented by connecting lines for each studied groups (---- for non-pregnant women; -- for normotensive pregnant and — for preeclamptic women).

while in normotensive pregnancy, a regulated condition predominates, as showed in Fig. 3.

In order to compare the inflammatory status between non-pregnant women *vs* normotensive pregnant or *vs* the severe PE group, the ascendant "cytokine signature" from the non-pregnant group was used as a reference curve (Fig. 4A). In this way, only the cytokine frequencies above the 50th percentile were considered. The ascendant "cytokine signature" analysis revealed that the normotensive group displayed an elevated percentage of women with high levels of IL-1β, IL-5 and IL-10, when compared to the non-pregnant group. These data suggest that healthy pregnancy is characterized by a predominant regulatory cytokine profile (Fig. 4A). Contrarily, the severe preeclamptic group showed a higher frequency of pro-inflammatory cytokines, including IL-8, IL-6, IL-1β, TNF-α, IL-12, and IFN-γ, comparing to the non-pregnant group (Fig. 4A). In physiological conditions, the cytokines balance is significantly altered in pregnancy by the placenta, since progesterone and cytokines modulate the immune cells by regulatory response [3]. The shift away from pro-inflammatory cytokine production during pregnancy is beneficial for this condition, since pro-inflammatory cytokines, especially IFN-γ and TNF-α, are harmful for pregnancy. Experimental studies revealed that these cytokines inhibited embryonic and fetal development [54,55] and interrupted pregnancy when injected into pregnant mice [54]. Several groups have shown that, particularly in the third trimester of human pregnancy, the ratio of pro-inflammatory/regulatory cytokines production by peripheral T-lymphocytes is decreased, as compared to non-pregnant women [56–60]. However, there is no consensus if this decreased cytokines pro-inflammatory/regulatory ratio is due to a decreased production of pro-inflammatory cytokines [59,60] or to an increased production of regulatory cytokines (IL-4, IL-5, IL-9, IL-10) [54]. Our results suggest an increased production of regulatory cytokines and a normal production of inflammatory cytokines in normotensive pregnant women.

In order to compare the inflammatory status between normotensive pregnant *vs* the severe PE group, the ascendant "cytokine signature" from the normotensive pregnant group was used as a reference curve (Fig. 4B). The severe preeclamptic group showed higher frequency of pro-inflammatory cytokines, including IL-8, IL-6, TNF-α, IL-12 and IFN-γ, along with lower frequency of regulatory cytokines (IL-5 and IL-10). Once more, our data suggest that severe PE evolves a high pro-inflammatory response and low participation of regulatory cytokines. Accordingly to our data, Sargent et al. has suggested that PE does not present a shift toward modulated response and, as a consequence, pro-inflammatory responses are not suppressed [61].

Correlation analysis was used as a tool to identify the dynamic connections within the pro-inflammatory cytokine network in preeclamptic women (Fig. 5). For the three groups studied, a positive correlation between IL-6 and IL-8 was found, suggesting that these cytokines participate in the physiological mechanisms. Normotensive pregnant and preeclamptic women showed a positive correlation between IL-8 and IL-1β, suggesting that these cytokines are normally expressed in pregnancy. However, a positive correlation between IL-6 and IL-1β was observed in normotensive pregnant, but not in preeclamptic women. On the other hand, a positive correlation between IL-8 and IFN-γ was observed in preeclamptic women, but not in normotensive pregnant. It is possible to infer that this change in cytokines profile can be an important factor for the development of PE. Besides, altered cytokine levels may have a direct effect on maternal systemic vasculature. In agreement with our data, Kalinderis et al. did not find a positive correlation between IL-6 and IL-1β in preeclamptic women [62].

In summary, our data showed that elevated levels of pro-inflammatory cytokines in the maternal circulation, with a deviation in the "IL-8 × IL-6" axis towards IFN-γ might drive the cytokine network in preeclamptic women towards an excessive systemic inflammatory state.

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